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Coated Medical Devices and Implants

The invention pertains to the field of coating medical devices and implants, which are used for treating proliferative diseases, such as, e.g., tumors or diseases of the arteriosclerotic group.

Cardiovascular diseases are diseases that occur widely in industrial nations. They represent one of the most frequent causes of death. In most cases, cardiovascular diseases are caused by arteriosclerosis. This is an inflammatory, fibroproliferative disease, which is responsible for 50% of all deaths in the USA, Europe and Japan (Ross 1993, Nature 362: 801-809). With its peripheral manifestation, it threatens the upkeep of the extremities; with its coronary manifestation, the risk of fatal myocardial infarction exists and with a supraortal attack creates the danger of stroke.

Treatment of arteriosclerosis is currently carried out in different ways. In addition to conservative measures (e.g., lowering the cholesterol level in the blood) and the bypass operation, mechanical dilation (angioplasty) as well as the intravascular removal of atheromatous tissue (atherectomy) of stenotic segments in peripheral arteries and the coronaries have been established as alternatives in regular clinical practice.

As explained below, the above-mentioned methods, however, are associated with a considerable number of drawbacks.

The value of the mechanically recanalizing process is greatly diminished by vessel occlusions because of vascular tears and dissections as well as acute thromboses (Sigwart et al. 1987, N. Engl. J. Med. 316: 701-706). The long-term success is jeopardized by the reoccurrence of constrictions (restenoses). The CAVEAT study on 1012 patients thus yielded that the restenosis rate six months after intervention in the case of coronary atherectomy amounted to 50% and was even 57% in the case of coronary angioplasty (Topol et al. 1993, N. Engl. J. Med. 329: 221-227). In addition, sudden vessel occlusions occurred in this study in 7% of the atherectomy patients and in 3% of the angioplasty patients. Nicolini and Pepine (1992, Endovascular Surgery 72: 919-940) report on a restenosis rate of between 35 and 40% and an acute occlusion rate of 4% after angioplastic operations.

To counteract these complications, different techniques were developed. This includes the implant of metallic endoprostheses (stents), (Sigwart et al. 1987, N. Engl. J. Med. 316: 701-706; Strecker et al., 1990, Radiology 175: 97-102). The stent implant in large-caliber arteries, e.g., in occlusions in the axis of the pelvis has already become a therapy procedure that is to be used primarily. The use of stents in the femoral arteries has shown disappointing results, however, with a primary openness rate of 49% and a reocclusion frequency of 43% (Sapoval et al., 1992, Radiology 184: 833-839). Unsatisfactory results mainly caused by restenosis were also achieved with previously available

stents in the coronary arteries (Kavas et al. 1992, J. Am. Coll. Cardiol 20: 467-474).

All previous pharmacological and mechanical interventions have not been able to prevent the restenosis up until now (Muller et al. 1992, J. Am. Coll. Cardiol. 19: 418-432).

The reason for the restenoses that frequently occur after mechanical interventions is assumed to be that the interventions induce proliferation and migration of smooth muscle cells in the vascular wall. The latter result in a neointimal hyperplasia and the observed restenoses in the vascular sections that are treated (Cascells 1992, Circulation 86: 723-729, Hanke et al. 1990, Circ. Res. 67: 651-659, Ross 1993, Nature 362: 801-809).

An alternative process for treatment of arteriosclerotic diseases is described by Sonobe et al. (Sonobe et al., The International Journal of Artificial Organs, Vol. 20 (6): 1997, 319-326). This process is named "Intracoronary Local Adhesive Delivery Technique"; it is the local application of adhesive agents on the site of the arteriosclerotic lesion. Cyanoacrylate monomer is preferably brought to the site of the lesion, which polymerizes there and in the most advantageous case forms a rigid tunnel along the arterial wall. This method has significant drawbacks, however. It requires, on the one hand, a lot of skill on the part of the attending physician, since cyanoacrylates can polymerize very quickly in the presence of moisture. Attention therefore must be paid to a quick, reliable and dry procedure. On the other hand, there is the danger that already polymerized cyanoacrylate again dissolves from the arterial wall or shortly

after application, a portion of the cyanoacrylate is elutriated which later sets in fine branches of the coronary vessels and thus can trigger a myocardial infarction. Further, it has been known for a long time from the literature that the monomeric cyanoacrylate irritates the tissue (Tseng et al., Medical Application of Cyanoacrylates as Surgical Adhesives, Japanese Journal of Artificial Organs; 18(1): 409-413; 1989).

There is therefore the object to make available medical devices and implants that can be used in the treatment of proliferative diseases, such as, e.g., arteriosclerosis or tumors and with whose help the drawbacks of the prior art are overcome.

This object is achieved by the medical implants that are described in the claims.

It has been found that medical implants that are coated with polymer mixtures, which contain polymers that consist of cyanoacrylate (polycyanoacrylic acid ester) or methylene malonic acid ester, prevent, surprisingly enough, the proliferation of smooth muscle cells or tumor cells and thus are extremely well suited for restenosis prophylaxis. Especially surprising in this case was the finding that -- as impressively shown in the examples -- very small amounts of polymeric cyanoacrylate are sufficient to produce a clearly antiproliferative effect in the two cell culture models studied (tumor cells and smooth muscle cells). The above-mentioned drawbacks in the local administration of cyanoacrylate monomer and subsequent polymerization in the blood vessel do not occur in the implants according to the invention since the cyanoacrylate is not used in

monomeric form, but rather in polymeric form. Consequently, it is ensured that when implants according to the invention are used, apart from the intended application site, undesirable polymer formation cannot occur. In addition, the tissue irritations that are known in the literature do not occur by the monomer when implants according to the invention are used. Moreover, possible operating problems based on the spontaneous tendency of cyanoacrylate monomer to polymerization in the presence of moisture -- such as, for example, the adhesion of administration instruments -- in the implants according to the invention are not possible. Further, the adhesion of the polymer to the surface of the implants is significantly better than on the body surface of the implant site (e.g., a luminal arterial surface). As a result, the risk of embolism by detaching polymer parts is avoided.

The production of the implants according to the invention is carried out, for example, in that a vehicle or an implant, such as, e.g., a stent, or the part of a medical implant that is to be coated is immersed in a solution that contains the polymer. The polymer remains on the vehicle after extraction or adheres to the implant and dries in the air. This type of production has the advantage that the coating of the implant can be done by the physician himself immediately before the implant according to the needs of the patient. For especially easy manageability, the sterile polymer solution can be made available in a special incubation vessel as a "pre-application kit."

Another variant for the production of the implants according to the invention is the CVD (Chemical Vapor Deposition) technique. In this case, the cyanoacrylate and/or the methylene malonic acid ester is vapor-deposited on the vehicle.

As a vehicle, the commercially available stents are suitable, such as, e.g., a Wiktor stent, a Palmaz-Schatz stent or a Strecker stent. The stents can consist of metal (e.g., nirosta steel) or a polymer (e.g., polyethylene terephthalate, silicone, polurethane urea). It is also possible to coat catheters and other medical devices with polymers that contain cyanoacrylate and/or methylene malonic acid ester.

The polymer layer that is applied on the vehicle should be between 5  $\mu\text{m}$  and 200  $\mu\text{m}$ . Layer thicknesses of between 20  $\mu\text{m}$  and 150  $\mu\text{m}$  are preferred.

Cyanoacrylate or methylene malonic acid ester can be used exclusively for polymerization and subsequent coating. Especially preferably used for polymerization is n-butyl-2-cyanoacrylate or cyanoacrylate butyl ester.

It is also possible to apply one of the polymers that consist of cyanoacrylate or methylene malonic acid ester together with other polymers on the vehicle, whereby the other polymers originate from one of the substance groups below:

proteins (especially albumin, gelatin, fibrinogen, fibrin, hirudin, heparin, collagen or immunoglobulin) as well as derivatives thereof (especially crosslinked polypeptides, conjugates of proteins with polyethylene glycols and other polymers), pseudopolyamino acids, starch or starch derivatives,

chitin, chitosan, pectin, polylactic acid, polyglycolic acid, polyhydroxybutyric acid, polyester, polycarbonates, polyamides, polyphosphazenes, polyvinyl alcohol, polyamino acids, poly- $\xi$ -caprolactone, polyorthoester, polyurethane, polyurea, polyethylene terephthalate.

Further, a polymer mixture that consists of cyanoacrylate and methylene malonic acid ester can also be used for coating.

In the case of all of these polymer mixtures, the proportion of cyanoacrylate or methylene malonic acid ester in the polymer layer that is placed on the implant should be between 100% and 10%. A content of cyanoacrylate or methylene malonic acid ester of 100% to 75% is preferred. A content of cyanoacrylate or methylene malonic acid ester of 100% to 80% is especially preferred.

The molecular weight of the polymer that is used lies in the range of 1,000 to 10,000,000 Dalton. The rate of degradation of the polymer can be controlled by its molecular weight. In addition, substances that influence the degradation of the polymer, such as, e.g., calcium carbonate, can also be contained in the polymer mixture.

Further, the polymer mixtures can contain still other additives, such as, e.g., softeners. Examples of softeners are, i.a., nonionic surfactants, such as nonylphenoxy-polyethylene oxide (Synperonic NP20), octoxynol (Triton X-100) or poloxamers (especially Pluronic F127 or Pluronic F68).

The examples below are to illustrate the subject of the invention without intending to be limited to this subject.

Example 1:

Production of polybutylcyanoacrylate by polymerization on interfaces.

5 g of butylcyanoacrylate (Sichel, Lot No. 82902065) is distributed uniformly by repeatedly rolling it around on the bottom of a glass crystallizing bowl ( $d = 47$  cm). The polymerizate is allowed to stand open for 2 days and then dissolved in THF by slight heating.

Example 2:

Production of polybutylcyanoacrylate by polymerization in ethanol/water.

4 ml of butylcyanoacrylate (Sichel, Lot. No. 82902065) is added with a syringe to 100 ml of ethanol/water (50%) while being stirred.

After two hours, 100 ml of water is added, and the polymer is filtered on a glass frit and air-dried. The powder is mixed with approximately 50 ml of methylene chloride and dissolved. The methylene chloride and the residual alcohol or water are removed by concentration by evaporation at 50°C. (Yield 3.6 g)

Example 3:

For coating a sample that is made of "medical grade" nirosta steel with the polymer that is produced according to Example 1,

the procedure is as follows:

1. 50 mg of poly-2-cyanoacrylic acid butyl ester that is produced according to Example 1 is dissolved in one ml of the solvent tetrahydrofuran (THF) by 2 hours of stirring at 40°C.

2. The sample of the "medical grade" nirosta steel that is purified with THF is drawn at a rate of one cm per second through the opening of the coating apparatus, which contains the above-mentioned polymer solution. In this case, a thin film of polymer solution is separated on the surface of the sample.

3. After the solvent is evaporated from the separated polymer solution (incubation at room temperature for 12 hours), a thin film that consists of poly-2-cyanoacrylic acid butyl ester remains on the sample.

4. A light-microscopic study yields a layer thickness of the separated poly-2-cyanoacrylic acid butyl ester film of about 30  $\mu\text{m}$ .

Example 4:

The therapeutic action of a "medical grade" nirosta steel sample that is coated with poly-2-cyanoacrylic acid butyl ester according to Example 3 is shown as follows:

1. LS174T cells (tumor cells) are cultured in a standard culture dish (DMEM medium with 10% fetal calf serum; 37°C; 5% carbon dioxide). This batch is used as a control without a "medical grade" nirosta steel sample that is coated with poly-2-cyanoacrylic acid butyl ester.

2. A "medical grade" nirosta steel sample that is coated with poly-2-cyanoacrylic acid butyl ester according to Example 1 and is 3 cm in length is attached to the bottom of the same with a magnet that is located on the outside of the culture dish. Then, the cultivated LS174T cells were moved to this culture dish.

3. Analogously to 2., a "medical grade" nirosta steel sample that was not coated with poly-2-cyanoacrylic acid butyl ester was introduced into a culture flask and attached magnetically there. Then, the cultivated LS174T cells were moved to this culture dish. This batch was used as a control with a "medical grade" nirosta steel sample, but without coating of the same with poly-2-cyanoacrylic acid butyl ester.

The state of the cells in batches 1. to 3. was monitored after 24 hours, 48 hours and 72 hours. As a criterion for evaluating the state of the cell cultures, the formation of a homogenous cellular film on the bottom of the culture flask was used.

The following findings were made:

In the batch described under 1.), the cells reproduced normally and formed an "almost homogeneous" cellular film. In the batch that was described under 2.), the state of the cell culture was significantly poorer after 24 hours. It had not formed any "almost homogeneous" cellular films. Also, no cells had grown even after 48 and 72 hours.

In the batch described under 3., the state of the cell culture was like in the control described under 1).

This study clearly shows that the coating of the "medical grade" nirosta steel sample with poly-2-cyanoacrylic acid butyl ester prevents the growth of cells.

Example 5:

The therapeutic action of a thin layer of poly-2-cyanoacrylic acid butyl ester that is applied to the inside surface of a glass dish that is produced according to Example 2, is shown as follows:

1. A10 cells (smooth muscle cells) are cultured in a sterile glass dish (diameter of 4 cm; height 1.5 cm) (30,000 cells per batch; DMEM medium with 10% fetal calf serum; 37°C; 5% carbon dioxide). This batch is used as a control without poly-2-cyanoacrylic acid butyl ester.
2. 0.5 ml of a solution that consists of 0.4% (w/w) of poly-2-cyanoacrylic acid butyl ester in THF is pipetted into a glass dish. The THF is evaporated at room temperature to separate a thin film that consists of 1.8 mg of poly-2-cyanoacrylic acid butyl ester in the glass dish. Then, the cultivated A10 cells were moved to this culture dish.
3. 0.5 ml of a solution that consists of 0.04% (w/w) poly-2-cyanoacrylic acid butyl ester in THF is pipetted into a glass dish. The THF is evaporated at room temperature to separate a thin film that consists of 0.18 mg of poly-2-cyanoacrylic acid butyl ester in the glass dish. Then, the cultivated A10 cells were moved to this culture dish.

4. 0.5 ml of a solution that consists of 0.004% (w/w) poly-2-cyanoacrylic acid butyl ester in THF is pipetted into a glass dish. The THF is evaporated at room temperature to separate a thin film that consists of 0.018 mg of poly-2-cyanoacrylic acid butyl ester in the glass dish. Then, the cultivated A10 cells were moved to this culture dish.

The state of the cells in batches 1.) to 4.) was monitored after 24 hours, 48 hours, and 72 hours. As a criterion for evaluating the state of the cell cultures, the numbers of living and dead cells were used, and their numbers were determined by light microscopy.

The following findings were made:

In the batch that is described under 1.), the cells in the glass dish grew well. An "almost homogeneous" cellular film was formed.

In the batches described under 2.) and 3.), no cells have grown.

In the batch that is described under 4.), a "slightly dense" cellular film (in comparison to control 1); has been formed.

This study clearly shows that with a thin layer of poly-2-cyanoacrylic acid butyl ester, the growth of the A10 cells can be prevented effectively and depending on the dose.

Example 6:

Coating of a medical implant with a polymer with use of a "kit" that contains the polymer

The kit consists of a glass vial (25 ml content, with resealable cap) that contains a 0.6% (w/w) poly-2-cyanoacrylic acid butyl ester (produced according to Example 1.) in THF. The medical implant (a stent with a metallic base) is removed from its packaging and introduced into the "kit vial" with the polymer solution under sterile conditions. The vial is sealed and lightly shaken several times to wet the stent uniformly with polymer solution. Then, the stent is removed from the vial under sterile conditions and dried under sterile conditions. The stent is now coated with polymer and is ready for use.

Example 7:

For coating a sample of "medical grade" nirosta steel with the polymer that is produced according to Example 1, the procedure is as follows:

The polymer solution is in a narrow cylindrical vessel. The "medical grade" nirosta steel samples that are purified with the solvent THF are immersed in the moderately viscous polymer solution and pulled out vertically at about 1 cm/second after a short incubation time (about 10-15 seconds). Excess polymer solution drips off downward, while a liquid film that is produced by viscosity on the surface of the "medical grade" nirosta steel sample remains. After intermediate drying under sterile conditions in air (20-22°C), a second immersion process is

carried out in the same way. After renewed intermediate drying, a third and last immersion process follows, whereupon the "medical grade" nirosta steel samples are completely dried. (Incubation at room temperature for 12 hours). A subsequent light-microscopic study yields a layer thickness of the separated poly-2-cyanoacrylic acid butyl ester film of about 50  $\mu\text{m}$ .

Example 8:

Production of polyethylcyanoacrylate by polymerization on interfaces

5 g of ethylcyanoacrylate (Sichel Company) is uniformly distributed by rolling it around on the bottom of a large crystallizing bowl ( $d = 47 \text{ cm}$ ). The polymerizate is allowed to stand open for 2 days and then dissolves in THF by slight heating.

Example 9:

Coating of a medical implant with a blend that consists of polymer and surfactant

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (1.5%) and nonionic surfactant (Synperonic NP20, ICI, 0.5%) in methylene chloride is produced. This mixture is used for coating a medical implant as is described in Example 3.

Example 10:

Coating of a medical implant with a blend that consists of polymer and surfactant

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (1.5%) and nonionic surfactant Triton X-100 (0.2%) in methylene chloride is produced. This mixture is used for coating a medical implant, as described in Example 3.

Example 11:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (1.5%) and nonionic surfactant Pluronic F127 in methylene chloride is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 12:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (1.5%) and nonionic surfactant Pluronic F68 in methylene chloride is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 13:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (0.3%) and polylactide-co-glycolide: Resomer RG503 (2.7%; Boehringer Ingelheim) in methylene chloride is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 14:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (0.6%) and poly-L-lactide resomer L 104 (2.4%; Boehringer Ingelheim) in methylene chloride is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 15:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (0.6%) and poly-D,L-lactide resomer R 503 (3.4%; Boehringer Ingelheim) in THF is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 16:

Coating a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (6.0%) and polyethylene glycol 5000 (0.18%; Fluka) in methylene chloride is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 17:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, 10 ml of a solution that consists of polybutylcyanoacrylate (8%) and an AB-block copolymer (2%) that consists of 98% poly-*e*-caprolactone and 2% polyethylene glycol 5000 (Birmingham Polymers) in methylene chloride is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 18:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, 10 ml of a solution that consists of polybutylcyanoacrylate (8%) and an AB-block copolymer (2%) that consists of 80% poly-*e*-caprolactone and 20% polyethylene glycol 5000 (Birmingham Polymers) in methylene chloride is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 19:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, 10 ml of a solution that consists of polybutylcyanoacrylate (8%) and an AB-block copolymer (2%) that consists of 70/30 D,L-polylactide-co-glycolides and PEG5000 (Inherent visc. = 0.68 dl/g, Birmingham Polymers) in methylene chloride is produced.

This mixture is used for coating a medical implant as described in Example 3.

Example 20:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, 10 ml of a solution that consists of polybutylcyanoacrylate (8%) and an AB-block copolymer (2%) that consists of 70/30 D,L-polylactide-co-glycolides and PEG5000 (Inherent Visc. = 0.94 dl/g, Birmingham Polymers) in THF is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 21:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, 5 ml of a solution that consists of polybutylcyanoacrylate (15%) in methylene chloride is produced. 5 ml of PEG-cyanoacrylate that contains another

polymer solution that is produced according to: Perrachia et al. Macromolecules 30: 846-851 (1997) in THF is added to this solution. This mixture is used for coating a medical implant as described in Example 3.

Example 22:

Coating of a medical implant with a polymer blend that consists of 2 polymers

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (10%) and polyvinyl alcohol (0.85%) in methylene chloride is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 23:

Coating of a medical implant with a mixture that consists of polybutylcyanoacrylate and a phospholipid.

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (9.0%) and the phospholipid DSPE-PEG5000 (Shearwater Polymers) in methylene chloride is produced. This mixture is used for coating a medical implant as described in Example 3.

Example 24:

Coating of a medical implant with a mixture that consists of polybutylcyanoacrylate and palmitic acid.

Under sterile conditions, a solution of 5 g of polybutylcyanoacrylate and 0.5 g of palmitic acid in 100 ml of

methylene chloride is produced. This solution is used for coating a medical implant as described in Example 3.

Example 25:

Coating of a medical implant with a polymer mixture with use of a "kit"

The kit consists of a glass vial (25 ml content; with resealable cap) that contains a polymer mixed solution that is produced according to Example 14 in THF. The medical implant (a stent with a metallic base) is removed from its packaging and introduced under sterile conditions into the "kit-vial" with the polymer mixed solution. The vial is sealed and lightly shaken several times to wet the stent uniformly with polymer mixed solution. Then, the stent is removed from the vial under sterile conditions and dried under sterile conditions. The stent is now coated with polymer and is ready for use.

Example 26:

Coating of a medical implant with a polymer and a basic adjuvant to control the polymer degradation.

Under sterile conditions, a solution that consists of polybutylcyanoacrylate (1.3%) in methylene chloride is produced. In this solution, 0.15% hydrobized  $\text{CaCO}_3$  microparticles (Winnofil, Zeneca) are finely dispersed with an Ultraturrax. This dispersion is used for coating a medical implant as described in Example 3.

Example 27:

Coating of a medical implant with a polymer

A methylene malonic acid dimethyl ester is produced according to De Kayser et al. (J. Org. Chem. 53, 4859-4862, 1988). 3 g of monomer is polymerized as in Example 1. A 2% solution in THF is produced and used for coating, as described in Example 3.

Example 28:

Coating of a medical implant with a polymer.

1 ml of the methylene malonic acid dimethyl ester of Example 26 is polymerized as in Lescure et al. (Pharm. Research 11(9), 1270-1277 (1994) by adding 100 ml of 1% dextran solution (MW = 70,000 Sigma) drop by drop at pH = 5.5 while being stirred. The nanoparticles that are obtained are washed 5 times by centrifuging from water, freeze-dried, and a 1% polymer solution in methylene chloride is produced from the lyophilizate and used for coating, as in Example 3.

Example 29:

Coating of a medical implant with a polymer.

1 ml of butylcyanoacrylate is polymerized by adding 100 ml of 1% dextran solution (MW = 70,000 Sigma) drop by drop at pH = 2.5 while being stirred. The nanoparticles that are obtained are washed 5 times by centrifuging from water, freeze-dried, and a 1% polymer solution in methylene chloride is produced from the lyophilizate and used for coating, as in Example 3.